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PATENT COOPERATION TREATY

From th
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

VEITENHEIMER, Erich E.
MORGAN, LEWIS & BOCKIUS LLP
1800 M Street, N.W.
Washington, D.C. 20036
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Applicant's or agent's file reference 44481-5044WO	Date of mailing *(day/month/year)* 16.11.2000
	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/17594	04/08/1999	04/08/1998

Applicant
COR THERAPEUTICS, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Emslander, S Tel.+49 89 2399-8718

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 44481-5044WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/17594	International filing date *(day/month/year)* 04/08/1999	Priority date *(day/month/year)* 04/08/1998
International Patent Classification (IPC) or national classification and IPC C12N15/00		
Applicant COR THERAPEUTICS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/03/2000	16.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Strobel, A Telephone No. +49 89 2399 7362

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/17594

I. Basis of th r port

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-17,19-26	as originally filed	
18	with telefax of	03/03/2000

Claims, No.:

1-27	as originally filed

Drawings, sheets:

1/13-13/13	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 15-20.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 15-20 are so unclear that no meaningful opinion could be formed (*specify*):
  see separate sheet
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   - ☐ the written form has not been furnished or does not comply with the standard.
   - ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack f unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-14, 21-27.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14, 21-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14, 21-27
Industrial applicability (IA)	Yes:	Claims	1-14, 21-27
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
s e separate sheet

Re Item I

Basis of the opinion

The priority claimed by the applicants seems to be valid.

The applicants filed amendments with telefax of 03.03.2000, replacing the erroneous oligonucleotide sequences of page 18 of the description with amended ones. However, these amendments will not be taken into consideration for the following reasons:
Since the applicants did not disclose said sequences elsewhere than on page 18 of the description (no sequence listings were filed with the application), it is not immediately evident that nothing else would have been intended as the correction than the amended sequences. Notably, it is not evident that the obvious error "5" occurring within the originally filed sequences has without doubt to be replaced by the corresponding bases of the amended oligonucleotides. Furthermore, none of the amended sequences is 100% identical to a stretch of the human or murine DNA GP V sequence - the applicants state themselves on page 17 of the description, last paragraph, that said primers are degenerate primers which are only based on the human GP V sequence. Thus, it is impossible to consider said new primer sequences as corrections of an obvious error.
The amendment is therefore considered as added matter and does not fulfil the requirements of Article 34(2)b PCT. According to Rule 70(2)c PCT this Written Opinion is based on the application as originally filed.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Lack of clarity of claims 15-20

None of said claims is limited to the modulation of a biological response which is attributable to the deletion of the GP V gene, thus going far beyond the underlying technical problem(s) of the alleged invention.
Furthermore, claims 15-20 concern a method for the identification of an agent that modulates a biological response of a nonhuman transgenic animal having a modified GP V gene. Said claims are not limited to a definable subject-matter. It is impossible for the man skilled in the art to define the nature of the agent. However, the technical

features of the claimed method depend strongly on the technical features of the agent. Furthermore, independent claim 15 and dependent claims 16 and 17 comprise any biological response to any kind of agent. This includes the infinite number of agents (natural substances, physiological substances, drugs etc.) that can elicit any kind of response, in fact this even comprises food, as it clearly modulates a biological response of the animal.
For these reasons, claims 15-20 are unclear and cannot be examined in a meaningful way (Article 6 PCT).

Re Item IV
Lack of unity of invention

1. The present application does not fulfil the requirements of unity of invention (Rule 13.1 PCT). The following groups of potential inventions have been recognized:

Group 1: Claims 1-14,23-27: a transgenic animal and cell lines derived therefrom; method for preparing said transgenic animal

Group 2: Claims 15-20: Method for identifying an agent that modulates a biological response in a transgenic animal

Rule 13.2 PCT stipulates that where a group of inventions is claimed the requirement of unity shall be fulfilled only where there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. "Special" technical features are those features that define a contribution which each of the inventions makes over the prior art. There is no special technical feature linking the different groups of claims mentioned above, since the method of claims 15-20 serves to identify agents that modify any kind of biological response, including responses that are not attributable to the modified expression of the GP V gene.

2. In view of the objections raised under III., V., and VIII., no objection of lack of unity is made by the examiner at this stage of the application. However, the applicant is informed that a unity objection may be made during the regional phase.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
Reference is made to the following documents:

D1: US 5 413 923 A (KUCHERLAPATI RAJU ET AL) 9 May 1995 (1995-05-09) cited in the application

D2: RAVANAT C ET AL.: "Gene cloning of rat and mouse platelet glycoprotein V: identification of megakaryocyte-specific promoters and demonstration of functional thrombin cleavage." BLOOD vol. 89, no. 9, 1 May 1997, pages 3253-3262 cited in the application
(A copy of D2 is attached to this Written Opinion)

For lack of clarity of the entire set of claims, see VIII.

1. This application relates to transgenic animals having a modified glycoprotein V gene, to methods of generating said animals and to cell lines containing a transgene and derived from said transgenic animals. Further claims concern a method of identifying an agent that modulates a biological response of said transgenic animal and a method for determining the effect of an agent on a characteristic of a transgenic animal attributable to the expression of the GP V gene.

2. **Inventive step of claims 1-14**
The underlying technical problem of said claims is to generate a nonhuman transgenic animal with an inactivated GP V gene (for the wording of "modified GP V gene" in claim 5 and "nonfunctional GP V gene" in claim 10, see VIII.). Said problem is solved by applying the standard technique for generating transgenic knock-out animals:

1. Obtaining murine GP V genomic DNA
2. Construction of a targeting vector (see figure 5)
3. Generation of ES cells carrying the construct in their genomic DNA
4. Generation of recombinant mice
5. Mating of founder chimeras with normal mice
6. Generation of GP V -/- offspring

The closest prior art for independent claim 1 is D2. D2 (cited on page 21, lines 1-2 of the application) discloses the cloning and biochemical characterization of the murine GP V gene and protein, respectively. D2 also states repeatedly that the results and molecular tools (namely, the nucleotide sequence of the murine GP V gene and vector constructs containing said gene) presented therein offer the possibility of generating transgenic animals, especially mice, carrying an inactivated GP V gene (page 3253, right column, second paragraph; page 3260, right column, second paragraph and third paragraph). This means that D2 states exactly the problem to be solved by claim 1.

The solution to this underlying technical problem is described by D1, where exactly the same standard method for generation of transgenic KO animals is disclosed in detail as in the application. D1 applies said standard method for the generation of ß2 microglobulin-deficient mice (columns 9-15, where all steps 1-5 are described). The only difference between D1 and claims 1-14 is the gene to be inactivated, ß2 microglobulin in D1 and GP V in the application. Despite the fact that said genes are not related one to the other, the man skilled in the art would inevitably arrive at the solution proposed in claims 1-14 by combining D1 with D2. The applicants confirm that the man skilled in the art willing to generate GP V KO mice would readily use the teaching of D1, since they disclose on page 9, lines 16-19 of the description that the homologous recombination techniques described in D1 could be used in order to generate GP V KO mice.

Thus, claims 1-14 are obvious and do not satisfy the requirements of Article 33(3) PCT.

3. Inventive step of claims 21-27

The features of the present claims 21-27 are either trivial or conventional in the art or within the competence of a skilled man seeking to improve the prior art processes mentioned in the search report and in the present opinion, so that the subject-matter of said claims also lacks an inventive step (Article 33(3) PCT).

Re Item VIII

Certain observations on the international application

1. **Lack of clarity of claims 1-9 and 15-25**
   Claims 1-9, and 15-25 contain the wording "modified GP V gene". It is though completely unclear what technical features could be implied by "modified gene". Thus, said claims are unclear (Article 6 PCT).

2. **Lack of clarity of claims 10-14, 26, and 27**
   Claims 10-14, 26, and 27 contain the wording "nonfunctional GP V gene". Similarly to point VIII.1., it is impossible to construe what technical features "nonfunctional" could imply. The function(s) of GP V remain(s) purely hypothetical, as can be derived from example 7 of the description, where the applicants speculate about biological functions of the GP V gene.
   Therefore, said claims also do not fulfil the requirements of Article 6 PCT.

3. **Lack of clarity and of support by the description of claims 20 and 21**
   Said claims concern a method for detecting the effect of an agent on a characteristic of a transgenic animal that is attributable to the expression of the GP V gene.
   Very much so as in III., it is impossible for the man skilled in the art to define the technical features of the agent, thereby being incapable of devising the claimed method.
   Furthermore, said claims are not supported by the description since the applicants only generated transgenic mice that lack the GP V gene. It is therefore impossible to assess effect of agents that are attributable to the expression of the GP V genes by using the teaching of the application.
   For these reasons, claims 20 and 21 do not satisfy the requirements of Article 6 PCT.

PCT/US99/175.

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MORGAN, LEWIS & BOCKIUS LLP

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

ADLER, Reid, G.
Morgan, Lewis & Bockius, LLP
1800 M Street, N.W.
Washington, DC 20036
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 30 September 1999 (30.09.99)	
Applicant's or agent's file reference 44481-5044WO	**IMPORTANT NOTIFICATION**
International application No. PCT/US99/17594	International filing date (day/month/year) 04 August 1999 (04.08.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 04 August 1998 (04.08.98)
Applicant COR THERAPEUTICS, INC. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
04 Augu 1998 (04.08.98)	60/109,797	US	24 Sept 1999 (24.09.99)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Carlos Naranjo

CRN

Telephone No. (41-22) 338.83.83

DOCKETED
By BSB Date 10-19-99

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MORGAN, LEWIS & BOCKIUS LLP

PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

To:

ADLER, Reid, G.
Morgan, Lewis & Bockius, LLP
1800 M Street, N.W.
Washington, DC 20036
ETATS-UNIS D'AMERIQUE

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year) 06 April 2000 (06.04.00)	
Applicant's or agent's file reference 44481-5044WO	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/US99/17594	04 August 1999 (04.08.99)	04 August 1998 (04.08.98)

Applicant
COR THERAPEUTICS, INC. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AL,AM,AT,AZ,BA,BB,BY,CH,CR,CU,DK,EE,ES,FI,GB,GD,GE,GH,GM,HR,
   HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,
   TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

DOCKETED
By RH Date 4/19/00

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No. (41-22) 740.14.35	Authorized officer: Christelle Croci Telephone No. (41-22) 338.83.38

Form PCT/IB/332 (September 1997)

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